## HIGHLIGHTS OF PRESCRIBING INFORMATION

**These highlights do not include all the information needed to use ONTAK safely and effectively. See full prescribing information for ONTAK.**

**ONTAK (denileukin diftitox) solution for intravenous use**
**Initial U.S. Approval: 1999**

**WARNING: SERIOUS INFUSION REACTIONS, CAPILLARY LEAK SYNDROME AND LOSS OF VISUAL ACUITY.**
**See full prescribing information for complete boxed warning.**

**The following adverse reactions have been reported:**

- **Serious and fatal infusion reactions. Administer Ontak in a facility equipped and staffed for cardiopulmonary resuscitation. (5.1)**
- **Capillary leak syndrome resulting in death. (5.2)**
- **Loss of visual acuity and color vision. (5.3)**

### RECENT MAJOR CHANGES

| | |
|---|---|
| Boxed Warning | 10/2008 |
| Warnings and Precautions (5.1, 5.2) | 10/2008 |

### INDICATIONS AND USAGE

Ontak is a CD25-directed cytotoxin indicated for the treatment of patients with persistent or recurrent cutaneous T-cell lymphoma whose malignant cells express the CD25 component of the IL-2 receptor. (1)

### DOSAGE AND ADMINISTRATION

- Premedicate with an antihistamine and acetaminophen prior to each Ontak infusion.
- Administer at 9 or 18 mcg/kg/day by intravenous infusion over 30 to 60 minutes for 5 consecutive days every 21 days for 8 cycles. (2.1, 2.2)

### DOSAGE FORMS AND STRENGTHS

- Single-use vial containing 150 mcg/mL (300 mcg in 2 mL) (3)

### CONTRAINDICATIONS

None.

### WARNINGS AND PRECAUTIONS

- **Infusion reactions:** Immediately stop and permanently discontinue Ontak for serious infusion reactions. Monitor patients following infusion. (5.1)
- **Capillary leak syndrome:** Monitor weight, edema, blood pressure and serum albumin levels. (5.2)
- **Loss of Visual Acuity and Color Vision:** Monitor visual acuity and color vision. (5.3)
- **Laboratory Tests:** Monitor serum albumin levels prior to the initiation of each treatment course. Delay administration of Ontak until serum albumin levels are at least 3.0 g/dL. (5.5)

### ADVERSE REACTIONS

The most common adverse reactions (≥20%) were pyrexia, nausea, fatigue, rigors, vomiting, diarrhea, headache, peripheral edema, cough, dyspnea and pruritus. (6)

**To report SUSPECTED ADVERSE REACTIONS, contact Eisai Inc. at 1-888-274-2378 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**

### DRUG INTERACTIONS

### USE IN SPECIFIC POPULATIONS

- **Pregnancy:** No human or animal data. Use only if clearly needed. (8.1)
- **Nursing Mothers:** Discontinue drug or nursing taking into consideration importance of drug to mother. (8.3)

**See 17 for PATIENT COUNSELING INFORMATION**

**Revised: 10/2008**

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**FULL PRESCRIBING INFORMATION: CONTENTS ***



*** Sections or subsections omitted from the full prescribing information are not listed**

**FULL PRESCRIBING INFORMATION**

**WARNING: SERIOUS INFUSION REACTIONS, CAPILLARY LEAK SYNDROME AND LOSS OF VISUAL ACUITY.**

**The following adverse reactions have been reported:**

- **Serious and fatal infusion reactions. Administer Ontak in a facility equipped and staffed for cardiopulmonary resuscitation. Immediately stop and permanently discontinue Ontak for serious infusion reactions [see *Warnings and Precautions (5.1)*].**
- **Capillary leak syndrome resulting in death. Monitor weight, edema, blood pressure and serum albumin levels prior to and during Ontak treatment [see *Warnings and Precautions(5.2)*].**
- **Loss of visual acuity and color vision [see *Warnings and Precautions(5.3)*].**

## 1. INDICATIONS AND USAGE

Ontak® is indicated for the treatment of patients with persistent or recurrent cutaneous T-cell lymphoma whose malignant cells express the CD25 component of the IL-2 receptor [see *Warnings and Precautions (5.4)*].

## 2. DOSAGE AND ADMINISTRATION

### 2.1. Dosing Schedule and Administration

- Premedicate with an antihistamine and acetaminophen prior to each Ontak infusion.
- Administer at 9 or 18 mcg/kg/day by intravenous infusion over 30-60 minutes for 5 consecutive days every 21 days for 8 cycles.
- Do **not** administer as a bolus injection.
- Withhold administration of Ontak if serum albumin levels are less than 3.0 g/dL.
- Discontinue for adverse infusion reactions.

### 2.2. Preparation and Administration

- Thaw vials in the refrigerator at 2 to 8°C (36 to 46°F) for not more than 24 hours or at room temperature for 1 to 2 hours.
- Bring Ontak to room temperature, before preparing the dose.
- Mix the solution in the vial by gentle swirling; do not shake.
- Visually inspect for particulate matter and discoloration prior to administration, whenever solution and container permit. Use only if the solution is clear, colorless and without visible particulate matter. After thawing, a haze may be visible which should clear when the solution is at room temperature.
- Do not refreeze Ontak after thawing.
- Prepare and hold diluted Ontak in plastic syringes or soft plastic IV bags. Do not use glass containers.
- Maintain concentration of Ontak at 15 mcg/mL or higher during all steps in the preparation of the solution for IV infusion.
- Withdraw the calculated dose from the vial(s) and inject it into an empty IV infusion bag. Do not add more than 9 mL of sterile saline without preservative to the IV bag for each 1 mL of Ontak.
- Do not mix Ontak with other drugs.
- Do not administer Ontak through an in-line filter.
- Administer prepared solutions of Ontak within 6 hours, using a syringe pump or IV infusion bag.
- Discard unused portions of Ontak immediately.

## 3. DOSAGE FORMS AND STRENGTHS

Single-use vial containing 150 mcg/mL (300 mcg in 2 mL)

## 4. CONTRAINDICATIONS

None.

## 5. WARNINGS AND PRECAUTIONS

### 5.1. Infusion Reactions

Infusion reactions, defined as symptoms occurring within 24 hours of infusion and resolving within 48 hours of the last infusion in that course, were reported in 70.5% (165/234) of Ontak-treated patients across 3 clinical studies utilizing the approved doses and schedule. Serious infusion reactions were reported in 8.1% (19/234) of Ontak-treated patients. There have been post-marketing reports of infusion reactions resulting in death.

For patients completing at least 4 courses of Ontak treatment in Study 1[see *Clinical Studies (14.1)*], the incidence of infusion reactions was lower in the 3rd and 4th cycles as compared to the 1st and 2nd cycles of Ontak.

Resuscitative equipment should be available during Ontak administration. Immediately stop and permanently discontinue Ontak for serious infusion reactions.

### 5.2. Capillary Leak Syndrome

Capillary leak syndrome was defined as the occurrence of at least 2 of the following 3 symptoms (hypotension, edema, serum albumin <3.0 g/dL) at any time during Ontak therapy. These symptoms were not required to occur simultaneously to be characterized as capillary leak syndrome. As defined, capillary leak syndrome was reported in 32.5% (76/234) of Ontak-treated patients. Among these 76 patients with capillary leak syndrome, one-third required hospitalization or medical intervention to prevent hospitalization. There have been post-marketing reports of capillary leak syndrome resulting in death.

The onset of symptoms in patients with capillary leak syndrome may be delayed, occurring up to 2 weeks following infusion. Symptoms may persist or worsen after the cessation of Ontak.

Regularly assess patients for weight gain, new onset or worsening edema, hypotension (including orthostatic changes) and monitor serum albumin levels prior to the initiation of each course of therapy and more often as clinically indicated. Withhold Ontak for serum albumin levels of less than 3.0 g/dL [see *Warnings and Precautions (5.5)*].

### 5.3. Visual Loss

Loss of visual acuity, usually with loss of color vision, with or without retinal pigment mottling has been reported following administration of Ontak. Recovery was reported in some of the affected patients; however, most patients reported persistent visual impairment.

### 5.4. CD25 Tumor Expression and Evaluation

Confirm that the patient's malignant cells express CD25 prior to administration of Ontak. A testing service for the assay of CD25 expression in tumor biopsy samples is available. For information on this service call 877-873-4724.

### 5.5. Laboratory Monitoring/Hypoalbuminemia

Monitor serum albumin levels prior to the initiation of each treatment course. Withhold administration of Ontak if serum albumin levels are less than 3.0 g/dL [see *Dosage and Administration (2.1)* and *Warnings and Precautions (5.2)*].

## 6. ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Infusion Reactions [see *Warnings and Precautions (5.1)*]
- Capillary Leak Syndrome [see *Warnings and Precautions (5.2)*]
- Visual Loss [see *Warnings and Precautions (5.3)*]

### 6.1. Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Safety data are available for 3 clinical studies in which 234 patients received Ontak at 9 mcg/kg (n=80) or 18 mcg/kg (n=154) at the recommended schedule. Of these studies, 1 was placebo-controlled and dose-ranging (Study 1, 100 Ontak-treated patients), one was a dose-comparison of 9 and 18 mcg/kg (Study 2, n=71), and the third was a single-arm study using 18 mcg/kg (n=63); all studies were limited to adult patients with CTCL. The median age of patients across the clinical studies was 60 years (range 23-91 years) and 36% (n=85) were 65 years of age or older; 55% were men and 85% were Caucasian.

Across all 3 studies, the most common adverse reactions in Ontak-treated patients (≥20%) were pyrexia, nausea, fatigue, rigors, vomiting, diarrhea, headache, peripheral edema, cough, dyspnea and pruritus. The most common serious adverse reactions were capillary leak syndrome (11.1%), infusion reactions (8.1%), and visual changes including loss of visual acuity (4%). Ontak was discontinued in 28.2% (66/234) of patients due to adverse reactions.

The data described in Table 1 reflect exposure to Ontak in 100 patients administered as a single agent at the recommended dosing schedule in the randomized placebo-controlled trial (Study 1). The median number of Ontak cycles was 7 (range 1-10) for the 9 mcg/kg cohort and 6 (range 1-11) for the 18 mcg/kg cohort. The median age of patients was 59 years (range 23-84 years) and 34% (n=34) were 65 years of age or older; 55% were men and 86% were Caucasian.

Table 1: Incidence of Adverse Reactions Occurring in ≥10% of Ontak-treated patients (18 mcg/kg group) and at a higher rate than Placebo in Study 1

| **MedDRA version 6.1 Preferred Term** | **Placebo N=44 n (%)** | **Ontak 9 mcg/kg N=45 n (%)** | **Ontak 18 mcg/kg N=55 n (%)** |
|---|---|---|---|
| Pyrexia | 7 (15.9) | 22 (48.9) | 35 (63.6) |
| Nausea | 10 (22.7) | 21 (46.7) | 33 (60.0) |
| Rigors | 9 (20.5) | 19 (42.2) | 26 (47.3) |
| Fatigue | 14 (31.8) | 21 (46.7) | 24 (43.6) |
| Vomiting | 3 (6.8) | 6 (13.3) | 19 (34.5) |
| Headache | 8 (18.2) | 13 (28.9) | 14 (25.5) |
| Edema peripheral | 10 (22.7) | 9 (20.0) | 14 (25.5) |
| Diarrhea | 4 (9.1) | 10 (22.2) | 12 (21.8) |
| Anorexia | 2 (4.5) | 4 (8.9) | 11 (20.0) |
| Rash | 2 (4.5) | 11 (24.4) | 11 (20.0) |
| Myalgia | 2 (4.5) | 8 (17.8) | 11 (20.0) |
| Cough | 3 (6.8) | 9 (20.0) | 10 (18.2) |
| Pruritus | 4 (9.1) | 7 (15.6) | 10 (18.2) |
| Back pain | 1 (2.3) | 7 (15.6) | 10 (18.2) |
| Asthenia | 2 (4.5) | 8 (17.8) | 10 (18.2) |
| Hypotension | 1 (2.3) | 3 (6.7) | 9 (16.4) |
| Upper respiratory tract infection | 5 (11.4) | 6 (13.3) | 7 (12.7) |
| Dizziness | 5 (11.4) | 5 (11.1) | 7 (12.7) |
| Arthralgia | 5 (11.4) | 7 (15.6) | 7 (12.7) |
| Pain | 3 (6.8) | 5 (11.1) | 7 (12.7) |
| Chest pain | 1 (2.3) | 2 (4.4) | 7 (12.7) |
| Dysgeusia | 1 (2.3) | 0 (0) | 6 (10.9) |
| Dyspnea | 2 (4.5) | 6 (13.3) | 6 (10.9) |

**Hepatobiliary Disorders:** Increase in serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) from baseline occurred in 84% of subjects treated with Ontak (197/234). In the majority of subjects, these enzyme elevations occurred during either the first or the second cycle; enzyme elevation resolved without medical intervention and did not require discontinuation of Ontak.

### 6.2. Immunogenicity

An immune response to denileukin diftitox was assessed using 2 enzyme-linked immunoassays (ELISA). The first assay measured reactivity directed against intact denileukin diftitox calibrated against anti-diphtheria toxin, and the second assay measured reactivity against the IL-2 portion of the protein. An additional *in vitro* cell-based assay that measured the ability of antibodies in serum to protect a human IL-2R-expressing cell line from toxicity by denileukin diftitox, was used to detect the presence of neutralizing antibodies which inhibited functional activity. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to the intact fusion protein denileukin diftitox. These results are highly dependent on the sensitivity and the specificity of the assays. Additionally, the observed incidence of the antibody positivity may be influenced by several factors, including sample handling, concomitant medication, and underlying disease. For these reasons, the comparison of the incidence of antibodies to denileukin diftitox with the incidence of antibodies to other products may be misleading.

In Study 1 [see *Clinical Studies (14.1)*], of 95 patients treated with denileukin diftitox, 66% tested positive for antibodies at baseline probably due to a prior exposure to diphtheria toxin or its vaccine. After 1, 2, and 3 courses of treatment, 94%, 99%, and 100% of patients tested positive, respectively. Mean titers of anti-denileukin diftitox antibodies were similarly increased in the 9 and 18 mcg/kg/day dose groups after 2 courses of treatment. Meanwhile, pharmacokinetic parameters decreased substantially ($C_{max}$~57%, AUC~80%), and clearance increased 2- to 8- fold.

In Study 2 [see *Clinical Studies (14.2)*], 131 patients were assessed for binding antibodies. Of these, 51 patients (39%) had antibodies at baseline. Seventy-six percent of patients tested positive after 1 course of treatment and 97% after 3 courses of treatment. Neutralizing antibodies were assessed in 60 patients; 45%, 73%, and 97% had evidence of inhibited functional activity in the cellular assay at baseline and after 1 and 3 courses of treatment, respectively.

## 7. DRUG INTERACTIONS
No formal drug-drug interaction studies have been conducted with Ontak.

## 8. USE IN SPECIFIC POPULATIONS

### 8.1. Pregnancy
It is not known whether Ontak can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Animal reproduction studies have not been conducted with Ontak. Ontak should be given to a pregnant woman only if clearly needed.

### 8.3. Nursing Mothers
It is not known whether Ontak is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from Ontak, a decision should be made whether to discontinue nursing or to discontinue Ontak, taking into account the importance of the drug to the mother.

### 8.4. Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

### 8.5. Geriatric Use
Clinical studies of Ontak did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects.

## 10. OVERDOSAGE
Doses of approximately twice the recommended dose (31 mcg/kg/day) resulted in moderate-to-severe nausea, vomiting, fever, chills and/or persistent asthenia.

## 11. DESCRIPTION
Ontak (denileukin diftitox), is a recombinant DNA-derived cytotoxic protein composed of the amino acid sequences for diphtheria toxin fragments A and B ($Met_1$-$Thr_{387}$)-His and the sequences for human interleukin-2 (IL-2; $Ala_1$-$Thr_{133}$). It is produced in an *E. coli* expression system and has a molecular weight of 58 kD. Neomycin is used in the fermentation process but is undetectable in the final product. Ontak is supplied in single use vials as a sterile, frozen solution intended for intravenous (IV) administration. Each 2 mL vial of Ontak contains 300 mcg of recombinant denileukin diftitox in a sterile solution of citric acid (20 mM), EDTA (0.05 mM) and polysorbate 20 (<1%) in Water for Injection, USP. The solution has a pH range of 6.9 to 7.2.

## 12. CLINICAL PHARMACOLOGY

### 12.1. Mechanism Of Action
Denileukin diftitox is a fusion protein designed to direct the cytocidal action of diphtheria toxin to cells which express the IL-2 receptor. *Ex vivo* studies report that after binding to the IL-2 receptor on the cell surface, denileukin diftitox is internalized by receptor-mediated endocytosis. The fusion protein is subsequently cleaved, releasing diphtheria toxin enzymatic and translocation domains from the IL-2 fragment, resulting in the inhibition of protein synthesis and ultimately, cell death.

### 12.3. Pharmacokinetics
Pharmacokinetic parameters associated with denileukin diftitox were determined over a range of doses (3 to 31 mcg/kg/day) in patients with lymphoma. Denileukin diftitox was administered as an IV infusion following the schedule used in the clinical trials. Following the first dose, denileukin diftitox displayed 2-compartment behavior with a distribution phase (half-life approximately 2 to 5 minutes) and a terminal phase (half-life approximately 70 to 80 minutes). Systemic exposure was variable but proportional to dose. Mean clearance was approximately 0.6 to 2.0 mL/min/kg and the mean volume of distribution was similar to that of circulating blood (0.06 to 0.09 L/kg). The mean clearance increased approximately 2- to 8-fold from course 1 to course 3 corresponding to a decrease in exposure of approximately 75%. No accumulation was evident between the first and fifth doses. Gender and age have no effect on pharmacokinetics of denileukin diftitox.

## 13. NONCLINICAL TOXICOLOGY

### 13.1. Carcinogenesis, Mutagenesis, Impairment of Fertility
There have been no studies to assess the carcinogenic potential of denileukin diftitox. Denileukin diftitox showed no evidence of mutagenicity in the Ames test and the chromosomal aberration assay. There have been no studies to assess the effect of denileukin diftitox on fertility.

## 14. CLINICAL STUDIES

### 14.1. Study 1: Placebo Controlled Study in CTCL (Stage Ia to III) Patients

The safety and efficacy of Ontak were evaluated in a randomized, double-blind, placebo-controlled, 3-arm trial in patients with Stage Ia to III CD25(+) CTCL. Eligible patients were required to have expression of CD25 on ≥ 20% of biopsied malignant cells by immunohistochemistry [see *Warnings and Precautions (5.4)*]. Patients were randomized to receive 0, 9 or 18 mcg/kg/day Ontak via intravenous infusion days 1-5 of each 21-day cycle, for up to 8 cycles. Randomization was stratified by disease stage (≤IIa vs. ≥IIb). The main efficacy outcome was objective response rate (ORR), using a Weighted Skin Severity Index, in conjunction with assessment of lymph node involvement and percentage of abnormal blood lymphocytes. A total of 144 patients were randomized: 44 patients to placebo, 45 patients to 9 mcg/kg/day Ontak and 55 patients to 18 mcg/kg/day Ontak. Randomization for the study was carried out at 1:1:1 for the first 73 patients, 4:1:4 for the next 31 patients, and 1:4:4 for the remaining 40 patients. The median age of patients was 59 years (range 23 to 84 years); 34% were ≥ 65 years. Fifty-five percent were men and 86% were Caucasian. Sixty-seven percent had early stage disease (≤ IIa). Patients had received a median of 2 anti-CTCL therapies (range 0 to 6) prior to study entry. Results for objective response rate (ORR) and progression-free survival (PFS) are shown in the table below.

Table 2: Efficacy Results in Study 1

| **Efficacy Endpoint** | **Ontak 18 mcg/kg/day (N = 55)** | **Ontak 9 mcg/kg/day (N = 45)** | **Placebo (N = 44)** |
|---|---|---|---|
| ORR %[a]<br>p-value[b] | 46%<br>p=0.002 | 37%<br>p=0.03 | 15%<br>-- |
| Median Response Duration | 220 days | 277 days | 81 days |
| PFS[c]<br>Hazard ratio<br>(95% CI)<br>p-value | 0.27<br>(0.14, 0.54)<br>p=0.0002 | 0.42<br>(0.20, 0.86)<br>p=0.02 | -- |

[a.] Adjusted for disease stage and changes in randomization ratios

[b.] Logistic regression model adjusting for disease stage and changes in randomization ratios over the course of the study; comparisons relative to placebo.

[c.] Cox regression analysis stratified by randomization ratio and adjusted for disease stage; comparisons relative to placebo.

### 14.2. Study 2: Dose Evaluation Study in CTCL (Stage IIb to IVa) Patients

A randomized, double-blind study was conducted to evaluate doses of 9 or 18 mcg/kg/day in 71 patients with recurrent or persistent, Stage Ib to IVa CTCL. Entry to this study required demonstration of CD25 expression on at least 20% of the cells in any relevant tumor tissue sample (skin biopsy) or circulating cells. Tumor biopsies were not evaluated for expression of other IL-2 receptor subunit components (CD122/CD132). Ontak was administered as an IV infusion daily for 5 days every 3 weeks. Patients received a median of 6 courses of Ontak therapy (range 1 to 11). The study population had received a median of 5 prior therapies (range 1 to 12) with 63% of patients entering the trial with Stage IIb or more advanced stage disease. The median age of patients was 64 years (range 26 to 91 years); 49% were ≥ 65 years. Fifty-two percent were men and 75% were Caucasian.

Overall, 30% (95% CI: 18-41%) of patients treated with Ontak experienced an objective tumor response (50% reduction in tumor burden which was sustained for ≥6 weeks; Table 3). Seven patients (10%) achieved a complete response and 14 patients (20%) achieved a partial response. The overall median duration of response, measured from first day of response, was 4 months with a median duration for complete response of 9 months and for partial response of 4 months.

Table 3: Efficacy Results in Study 2

| **Clinical Response** | **9 mcg/kg/day** | **18 mcg/kg/day** |
|---|---|---|
| Complete Response<br>95% Confidence Interval | 9% (3/35)<br>(2%, 23%) | 11% (4/36)<br>(3%, 26%) |
| Partial Response<br>95% Confidence Interval | 14% (5/35)<br>(9%, 30%) | 25% (9/36)<br>(12%, 42%) |
| Overall Response<br>95% Confidence Interval | 23% (8/35)<br>(10%, 40%) | 36% (13/36)<br>(21%, 54%) |

## 16. HOW SUPPLIED/STORAGE AND HANDLING

Ontak is supplied as 150 mcg/ml, sterile, frozen solution (300 mcg in 2 mL) in a sterile single-use vial.

NDC 62856-603-01, 6 vials in a package.
Store frozen at or below -10°C (14°F).
Manufactured by:
Eisai Medical Research Inc.
Ridgefield Park, NJ 07660
US License No. 1763
Manufactured at:
Hollister-Stier Labs LLC
Spokane, WA 99207
Distributed by:
Eisai Inc.
Woodcliff Lake, NJ 07677

**17. PATIENT COUNSELING INFORMATION**

Advise patients to report:

- Fever, chills, breathing problems, chest pain, tachycardia, and urticaria following infusion.
- Rapid weight gain, edema, and orthostatic hypotension following infusion. Instruct patients to weigh themselves daily.
- Visual loss, including loss of color vision.